Docket No.: PF-0525 USN

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By: Diane Kizer Printed: Diane Kizer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

Title: HUMAN SOCS PROTEINS

Serial No.: 09/701,232 Filing Date: July 05, 2001

Examiner: Hamud, F. Group Art Unit: 1647

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL FEE SHEET

Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard;
2. Submission of Executed Declaration (1 pg.);
3. Executed Declaration of Lars Michael Furness (12 pp.); and
4. Executed Declaration of Dr. Tod Bedilion (15 pp.).

The fee has been calculated as shown below.

X No additional Fee is required.

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 09-0108. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,

INCYTE CORPORATION

Date: July 11, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Submission of Executed Declaration Under 37 C.F.R. § 1.132

Submitted herewith are executed copies of the declarations of Dr. Tod Bedilion and Lars Michael Furness under 37 C.F.R. § 1.132 to replace the unsigned copies thereof which were submitted on June 23, 2003.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: July 11, 2003

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Docket No.: PF-0525 USN

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

Title:	HUMAN SOCS PROTEINS		
Serial No.:	09/701,232	Filing Date:	July 5, 2001
Examiner:	Hamud, F.	Group Art Unit:	1647

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF LARS MICHAEL FURNESS UNDER 37 C.F.R. § 1.132

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside, Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Corporation (hereinafter "Incyte") as a Director of Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to Incyte Corporation.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry) from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du

Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics, and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, western and northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

In 1998, I moved to Incyte Genomics, Inc., to the Pharmacogenomics group to look at the application of genomics and proteomics to the pharmaceutical industry. In 1999, I was appointed director of the LifeExpress Lead Program which used microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improved drug design and development.

On December 12, 2001 I founded Nuomics Consulting Ltd., in Exning, U.K., and I am currently employed as Managing Director. Nuomics Consulting Ltd. provides expert technical knowledge and advice to businesses around the areas of genomics, proteomics, pharmacogenomics, toxicogenomics and chemogenomics.

3. I have reviewed the specification of a United States patent application that I understand was filed on July 5, 2001 in the names of Preeti Lal et al. and was assigned Serial No. 09/701,232 (hereinafter "the Lal '232 application"). Furthermore, I understand that this United States patent application is the National Stage of International Application No. PCT/US99/11497, filed May 25, 1999, and published in English as WO 99/61614 on December 2, 1999, which claims the benefit under 35 U.S.C. § 119(e) of provisional applications U.S. Ser . No. 60/087,104, filed May 28, 1998 (hereinafter the Lal '104 application) and U.S. Ser. No. 60/150,701, filed December 17, 1998. The provisional applications provide support for what is disclosed in the instant Lal '232 application. The SEQ ID NO:5 and SEQ ID NO:14 sequences recited in the Lal '232 application claims were first disclosed in the Lal '104 application and listed as SEQ ID NO:5 and SEQ ID NO:11, respectively, in the Lal '104 application. My remarks herein will therefore be directed to the Lal '104 patent application, and May 28, 1998, as the relevant date of filing. In broad overview, the Lal '104 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene and protein expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Lal '232 application contains claims that are directed to a isolated polypeptide comprising the amino acid sequence of SEQ ID NO:5 (hereinafter "the SEQ ID NO:5 polypeptide"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Lal '232 application does not disclose a specific and substantial asserted utility or a well established utility for the claimed SEQ ID NO:5 polypeptide. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Lal '232 application and its priority application, the Lal '104 application, do not disclose a specific and substantial asserted utility or a well established "real-world" utility for the claimed SEQ ID NO:5 polypeptide, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Lal '104 application pertains on May 28, 1998, would have concluded that the Lal '104 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:5 polypeptide in its then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Lal '104 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:5 polypeptide. More specifically, persons skilled in the art on May 28, 1998 would have understood the Lal '104 application to disclose the use of the SEQ ID NO:5 polypeptide as a research tool in a number of gene and protein expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Lal '104 application, and (b) a number of published articles and patent documents that evidence gene and protein expression monitoring techniques that were well-known before the May 28, 1998 filing date of the Lal '104 application. The published articles and patent documents I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G., A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter "the Anderson 1991 article") (copy annexed at Tab A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L., Raymackers, J., Steiner, S. Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1981 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D., Humphery-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B., Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G., Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions, Electrophoresis, 15, 529-539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F); and

(g) Large Scale Biology Company Info; LSB and LSP Information; from http://www.lsbc.com (2001) (copy annexed at Tab G).

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in protein expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Lal '104 application on May 28, 1998 would have understood that application to disclose the SEQ ID NO:5 polypeptide to be useful for a number of gene and protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

Furthermore, items (a)-(f) establish that protein two-dimensional polyacrylamide gel electrophoresis and western blot analysis were well-known and established methods routinely used in toxicology testing and drug development at the time of filing the Lal '104 application and for several years prior to May 28, 1998. As such, one of ordinary skill in the art would have recognized that the polypeptide of SEQ ID NO:5 could be used in toxicology testing and drug development, irrespective of its biochemical activities.

9. The SEQ ID NO:5 and SEQ ID NO:14 sequences recited in the Lal '232 application claims were first disclosed in the Lal '104 application and listed as SEQ ID NO:5 and SEQ ID NO:11, respectively, in the Lal '104 application. The SEQ ID NO:5 polypeptide is referred to as HSCOP-5 in the Lal '232 application and as SOCP-5 in the Lal '104 application. Turning more specifically to the Lal '104 specification, the SEQ ID NO:5 polypeptide is shown at pages 46-47 under the heading "Sequence Listing." The Lal '104 specification specifically teaches that the "invention features substantially purified polypeptides, human SOCS proteins , referred to collectively as 'SOCP' and individually as 'SOCP-1', 'SOCP-2', 'SOCP-3', 'SOCP-4', 'SOCP-5', and 'SOCP-6' and that the "invention provides a substantially purified polypeptide

comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 (SEQ ID NO:1 through 6). . . " (Lal '104 application at page 2, lines 32-36). It further teaches that (a) the identity of the SEQ ID NO:5 polypeptide was determined from a uterus tissue cDNA library (UTRSNOR01) (Lal '104 application, Tables 1 and 4), (b) the SEQ ID NO:5 polypeptide is the human SOCS protein referred to as "SOCP-5" and is encoded by SEQ ID NO:11. (Lal '104 application at page 2, lines 31-36 and Table 1), and (c) northern analysis of SEQ ID NO:11 shows its expression predominantly in cDNA libraries made from reproductive, cardiovascular, hematopoietic/immune, cancer-associated, inflammation-associated, and fetal tissues (Lal '104 application at Table 3) and therefore "SOCP appears to play a role in cancer, immune disorders, and infectious diseases." (Lal '104 application at page 20, lines 22-23.)

The Lal '104 application discusses a number of uses of the SEQ ID NO:5 polypeptide in addition to its use in gene and protein expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Lal '104 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:5 polypeptide. Consequently, my discussion in this Declaration concerning the Lal '104 application focuses on the portions of the application that relate to the use of the SEQ ID NO:5 polypeptide in gene and protein expression monitoring applications.

10. The Lal '104 application discloses that the polynucleotide sequences disclosed therein, including the polynucleotides encoding the SEQ ID NO:5 polypeptide, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used "for the detection and/or quantification of nucleic acid or protein sequences." (Lal '104 application at page 18, lines 27-28.)

The Lal '104 application also discloses that the SEQ ID NO:5 polypeptide is useful in other protein expression detection technologies. The Lal '104 application states that "[i]mmunological methods for detecting and measuring the expression of SOCP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)." (Lal '104 application at page 18, lines 29-32.) Furthermore, the Lal '104 application discloses that "[a] variety of protocols for measuring SOCP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of SOCP expression. Normal or standard values for SOCP expression are established by combining body fluids or cell extracts taken from normal

mammalian subjects, preferably human, with antibody to SOCP under conditions suitable for complex formation." (Lal '104 application at page 28, lines 5-9.)

In addition, at the time of filing the Lal '104 application, it was well known in the art that gene and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, and as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at page 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted to a series of identified proteins based upon amino acid chain length (Tab A at page 911) and how that standard curve can be used in protein expression analysis. The Anderson 1991 article teaches that "there is a long-term need for a comprehensive database of liver proteins" (Tab A at page 912).

The Wilkins article is one of a number of documents that were published prior to the May 28, 1998 filing date of the Lal '104 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Lal '104 application, the Wilkins article, and other related pre-May 28, 1998 publications, persons skilled in the art on May 28, 1998 clearly would have understood the Lal '104 application to disclose the SEQ ID NO:5 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development on May 28, 1998 (and for many years prior to May 28, 1998) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of

the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr Leigh Anderson to found the Large Scale Biology Corporation in 1985, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pages 1, 3, and 5).

Accordingly, the teachings in the Lal '104 application, in particular regarding use of SEQ ID NO:5 in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly include toxicity studies and persons skilled in the art who read the Lal '104 application on May 28, 1998 would have understood that to be so.

11. As previously discussed (*supra*, paragraphs 7 and 8), my experience with protein analysis methods in the mid-1980s and the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the May 28, 1998 filing date of the Lal '104 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information.... -- among others, ... drug development and testing" (See Tab D, page 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Lal '104 application clearly discloses that expression of SOCP-5 is associated with reproductive, cardiovascular, hematopoietic/immune, cancer-associated, inflammation-associated, and fetal tissues (Lal '104 application at Table 3). The Bjellqvist article showed that a protein may be identified accurately by its positional co-ordinates, namely molecular mass and isoelectric point (See Tab F). The Lal '104 application clearly disclosed SEQ ID NO:5 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

12. A person skilled in the art on May 28, 1998, who read the Lal '104 application, would understand that application to disclose the SEQ ID NO:5 polypeptide to be highly useful in analysis of differential expression of proteins. For example, the specification of the Lal '104 application would have led a person skilled in the art on May 28, 1998 who was using protein expression monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, and infectious diseases to conclude that a 2-D PAGE map that used the isolated SEQ ID NO:5 polypeptide would be a highly useful tool and to

request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:5 polypeptide sequence. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:5 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, and infectious diseases for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(b) below a number of reasons why a person skilled in the art, who read the Lal '104 specification on May 28, 1998, would have concluded based on that specification and the state of the art at that time, that SEQ ID NO:5 polypeptide would be a highly useful tool for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for cancer, immune disorders, and infectious diseases by means of 2-D PAGE maps, as well as for other evaluations:

(a) The Lal '104 specification contains a number of teachings that would lead persons skilled in the art on May 28, 1998 to conclude that a 2-D PAGE map that utilized the isolated SEQ ID NO:5 polypeptide would be a more useful tool for protein expression monitoring applications relating to drugs for treating cancer, immune disorders, and infectious diseases than a 2-D PAGE map that did not use the SEQ ID NO:5 polypeptide sequence. Among other things, the Lal '104 specification teaches that (i) the identity of the SEQ ID NO:5 polypeptide was determined from a "uterus tissue cDNA library (UTRSNOR01)," (Lal '104 application, Tables 1 and 4) (ii) the SEQ ID NO:5 polypeptide is the human SOCS protein referred to as "SOCP-5" (listed as HSCOP-5 in the Lal '232 application) (Lal '104 application at page 2, lines 31-36 and Table 1), and (iii) SEQ ID NO:11 (listed as SEQ ID NO:14 in the Lal '232 application) is expressed predominantly in cDNA libraries made from reproductive, cardiovascular, hematopoietic/immune, cancer-associated, inflammation-associated, and fetal tissues (Lal '104 application at Table 3) and therefore "SOCP appears to play a role in cancer, immune disorders, and infectious diseases." (Lal '104 application at page 20, lines 22-23; see paragraph 9, *supra*). The isolated polypeptide could therefore be used as a control to more accurately gauge the expression of SOCP-5 (listed as HSCOP-5 in the Lal '232 application) in the sample and consequently more accurately gauge the affect of a toxicant on expression of the gene.

(b) Persons skilled in the art on May 28, 1998 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized a

SEQ ID NO:5 polypeptide would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the SEQ ID NO:5 polypeptide and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on May 28, 1998, having read the Lal '104 specification, would specifically request that any 2-D PAGE map that was being used for conducting protein expression monitoring studies on drugs for treating cancer, immune disorders, and infectious diseases (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the SEQ ID NO:5 polypeptide sequence. Persons skilled in the art on May 28, 1998 would have wanted their 2-D PAGE map to utilize the SEQ ID NO:5 polypeptide sequence because a 2-D PAGE map that utilized protein sequence information the polypeptide (as compared to one that did not) would provide more useful results in the kind of protein expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to May 28, 1998.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Lal '104 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:5 polypeptide.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Lal '104 disclosure regarding the uses of the SEQ ID NO:5 polypeptide for protein expression monitoring applications is <u>not</u> limited to the use of that protein in 2-D PAGE maps. For one thing, the Lal '104 disclosure regarding the technique used in gene and protein expression monitoring applications is broad. (Lal '104 application at, e.g., page 18, lines 24-28.)

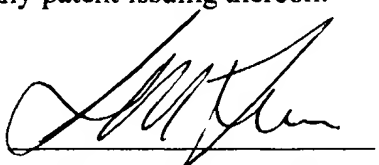
In addition, the Lal '104 specification repeatedly teaches that the protein described therein (including the SEQ ID NO:5 polypeptide) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

(a) Lal '104 application at page 18, lines 29-32 ("Immunological methods for detecting and measuring the expression of SOCP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS).");

(b) Lal '104 application at page 28, lines 5-12 ("A variety of protocols for measuring SOCP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of SOCP expression. Normal or standard values for SOCP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to SOCP under conditions suitable for complex formation The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of SOCP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.").

Thus a person skilled in the art on May 28, 1998, who read the Lal '104 specification, would have routinely and readily appreciated that the SEQ ID NO:5 polypeptide disclosed therein would be useful to conduct protein expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Lal '104 application. For example, a person skilled in the art on May 28, 1998 would have routinely and readily appreciated that the SEQ ID NO:5 polypeptide would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of cancer, immune disorders, and infectious diseases, and (b) analyses of the efficacy and toxicity of such drugs.

14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



L. Michael Furness, B.Sc.

Signed at Exning, United Kingdom
this 30th day of June, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

Title:	HUMAN SOCS PROTEINS		
Serial No.:	09/701,232	Filing Date:	July 5, 2001
Examiner:	Hamud, F.	Group Art Unit:	1647

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. TOD BEDILION
UNDER 37 C.F.R. § 1.132

I, TOD BEDILION, a citizen of the United States, residing at 132 Winding Way, San Carlos, California, declare that:

1. I was employed by Incyte Corporation (hereinafter "Incyte") as a Director of Corporate Development until May 11, 2001. I am currently under contract to be a Consultant to Incyte Corporation.

2. In 1996, I received a Ph.D. degree in Cell, Molecular and Development Biology from UCLA. I had previously received, in 1988, a B.S. degree in biology from UCLA.

Upon my graduation from UCLA, I became, in April 1996, the first employee of Synteni, Inc. (hereinafter "Synteni"). I was a Research Director at Synteni from April 1996 until Synteni was acquired by Incyte in early 1998.

I understand that Synteni was founded in 1994 by T. Dari Shalon while he was a graduate student at Stanford University. I further understand that Synteni was founded for the purpose of commercially exploiting certain "cDNA microarray" technology that was being worked on at Stanford in the early to mid-1990s. That technology, which I will sometimes refer to herein as the "Stanford-developed cDNA microarray technology," was the subject of Dr. Shalon's doctoral thesis at Stanford. I understand and believe that Dr. P.O. Brown was Dr. Shalon's thesis advisor at Stanford.

During the period beginning before I was employed by Synteni and ending upon its acquisition by Incyte in early 1998, I understand Synteni was the exclusive licensee of the

Stanford-developed cDNA microarray technology, subject to any right that the United States government may have with respect to that technology. In early 1998, I understand Incyte acquired rights under the Stanford-developed cDNA microarray technology as part of its acquisition of Synteni.

I understand that at the time of the commencement of my employment at Synteni in April 1996, Synteni's rights with respect to the Stanford-developed cDNA technology included rights under a United States patent application that had been filed June 7, 1995 in the names of Drs. Brown and Shalon and that subsequently issued as United States Patent No. 5,807,522 (the Brown '522 patent). In December 1995, the subject matter of the Brown '522 patent was published based on a PCT patent application that had also been filed in June 1995. The Brown '522 patent (and its corresponding PCT application) describes the use of the Stanford-developed cDNA technology in a number of gene expression monitoring applications, as will be discussed more fully below.

Upon Incyte's acquisition of Synteni, I became employed by Incyte. From early 1998 until late 1999, I was an Associate Research Director at Incyte. In late 1999, I was promoted to the position of Director, Corporate Development.

I have been aware of the Stanford-developed cDNA microarray technology since shortly before I commenced my employment at Synteni. While I was employed by Synteni, virtually all (if not all) of my work efforts (as well as the work efforts of others employed by Synteni) were directed to the further development and commercial exploitation of that cDNA microarray technology. By the end of 1997, those efforts had progressed to the point that I understand Incyte agreed to pay at least about $80 million to acquire Synteni. Since I have been employed by Incyte, I have continued to work on the further development and commercial exploitation of the cDNA microarray technology that was first developed at Stanford in the early to mid-1990s.

3. I have reviewed the specification of a United States patent application that I understand was filed on July 5, 2001 in the names of Preeti Lal et al. and was assigned Serial No. 09/701,232 (hereinafter "the Lal '232 application"). Furthermore, I understand that this United States patent application is the National Stage of International Application No. PCT/US99/11497, filed May 25, 1999, and published in English as WO 99/61614 on December 2, 1999, which claims the benefit under 35 U.S.C. § 119(e) of provisional applications U.S. Ser . No. 60/087,104, filed May 28, 1998 (hereinafter the Lal '104 application) and U.S. Ser. No. 60/150,701, filed December 17, 1998. The provisional applications provide support for what is disclosed in the instant Lal '232 application. The SEQ ID NO:5 and SEQ ID NO:14 sequences recited in the Lal '232 application claims were first disclosed in the Lal '104 application and listed as SEQ ID NO:5 and SEQ ID NO:11, respectively, in the Lal '104 application. My

remarks herein will therefore be directed to the Lal '104 patent application, and May 28, 1998, as the relevant date of filing. In broad overview, the Lal '104 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of cancer, immune disorders, and infectious diseases), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Lal '232 application contains claims that are directed to an isolated polynucleotide comprising the polynucleotide sequence of SEQ ID NO:14 (hereinafter "the SEQ ID NO:14 polynucleotide"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Lal '232 application does not disclose a specific and substantial asserted utility or a well established utility for the claimed SEQ ID NO:14 polynucleotide. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Lal '232 application and its priority application, the Lal '104 application, do not disclose a specific and substantial asserted utility or a well established "real-world" utility for the claimed Lal '232 application SEQ ID NO:14 polynucleotide, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Lal '104 application pertains on May 28, 1998 would have concluded that the Lal '104 application disclosed, for the benefit of the public, a specific beneficial use of the Lal '232 application SEQ ID NO:14 polynucleotide in its then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address

whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Lal '104 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed Lal '232 application SEQ ID NO:14 polynucleotide. More specifically, persons skilled in the art on May 28, 1998 would have understood the Lal '104 application to disclose the use of the Lal '232 application SEQ ID NO:14 polynucleotide in a number of gene expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-16 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Lal '104 application, and (b) a number of published articles and patent documents that evidence gene expression monitoring techniques that were well-known before the May 28, 1998 filing date of the Lal '104 application. The published articles and patent documents I considered are:

(a) Schena, M., Shalon, D., Heller, R., Chai, A., Brown, P.O., and Davis, R.W., Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes, Proc. Natl. Acad. Sci. USA, 93, 10614-10619 (1996) (hereinafter "the Schena 1996 article") (copy annexed at Tab A);

(b) Schena, M., Shalon, D., Davis, R.W., Brown, P.O., Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray, Science, 270, 467-470 (1995) (hereinafter "the Schena 1995 article") (copy annexed at Tab B);

(c) Shalon and Brown PCT patent application WO 95/35505 titled "Method and Apparatus For Fabricating Microarrays Of Biological Samples," filed on June 16, 1995, and published on December 28, 1995 (hereinafter "the Shalon PCT application") (copy annexed at Tab C);

(d) Brown and Shalon U.S. Patent No. 5,807,522, corresponding to the Shalon PCT application, titled "Methods For Fabricating Microarrays Of Biological Samples," filed on June 7, 1995 and issued on September 15, 1998 (hereinafter "the Brown '522 patent") (copy annexed at Tab D);

(e) DeRisi, J., Penland, L., and Brown, P.O. (Group 1); Bittner, M.L., Meltzer, P.S., Ray, M., Chen, Y., Su, Y.A., and Trent, J.M. (Group 2), Use of a cDNA microarray to analyse gene expression patterns in human cancer, Nat. Genet., 14(4), 457-460 (1996) (hereinafter "the DeRisi article") (copy annexed at Tab E);

(f) Shalon, D., Smith, S.J., and Brown, P.O., A DNA Microarray System for Analyzing Complex DNA Samples Using Two-color Fluorescent Probe Hybridization, Genome Res., 6(7), 639-645 (1996) (hereinafter "the Shalon article") (copy annexed at Tab F);

(g) Heller, R.A., Schena, M., Chai A., Shalon, D., Bedilion, T., Gilmore, J., Woolley, D.E., and Davis R.W., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA, 94, 2150-2155 (1997) (hereinafter "the Heller article")(copy annexed at Tab G); and

(h) Sambrook, J., Fritsch, E.F., Maniatis, T., Molecular Cloning, A Laboratory Manual, pages 7.37 and 7.38, Cold Spring Harbor Press (1989) (hereinafter "the Sambrook Manual") (copy annexed at Tab H).

8. Many of the published articles and patent documents I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to work done at Stanford University in the early and mid-1990s with respect to the development of cDNA microarrays for use in gene expression monitoring applications under which Synteni became exclusively licensed. As I will discuss, a person skilled in the art who read the Lal '104 application on May 28, 1998 would have understood that application to disclose the Lal '232 application SEQ ID NO:14 polynucleotide to be useful for a number of gene expression monitoring applications, e.g., as a probe for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford.

Furthermore, items (a)-(g) establish that gene expression monitoring applications utilizing cDNA microarrays were well-known and established methods routinely used in toxicology testing and drug development at the time of filing the Lal '104 application and for several years prior to May 28, 1998. As such, one of ordinary skill in the art would have recognized that the Lal '232 application SEQ ID NO:14 polynucleotide could be used in toxicology testing and drug development, irrespective of the biochemical activities of the encoded polypeptide.

9. The SEQ ID NO:5 and SEQ ID NO:14 sequences recited in the Lal '232 application claims were first disclosed in the Lal '104 application and listed as SEQ ID NO:5 and SEQ ID NO:11, respectively, in the Lal '104 application. The SEQ ID NO:5 polypeptide is

referred to as HSCOP-5 in the Lal '232 application and as SOCP-5 in the Lal '104 application. Turning more specifically to the Lal '104 specification, the SEQ ID NO:5 polypeptide and the SEQ ID NO:11 polynucleotide are shown at pages 46-47 and 51-52, respectively, under the heading "Sequence Listing." The Lal '104 specification specifically teaches that the "invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12 (SEQ ID NO:7 through 12) . . . "] (Lal '104 application at page 3, lines 13-15.) It further teaches that (a) the identity of the SEQ ID NO:11 polynucleotide was determined from a uterus tissue cDNA library (UTRSNOR01) (Lal '104 application, Tables 1 and 4), (b) the SEQ ID NO:11 polynucleotide encodes the human SOCS protein (SOCP-5) shown as SEQ ID NO:5 (Lal '104 application at page 2, lines 32-36 and Table 1), and (c) northern analysis of SEQ ID NO:11 shows its expression predominantly in cDNA libraries made from reproductive, cardiovascular, hematopoietic/immune, cancer-associated, inflammation-associated, and fetal tissues (Lal '104 application at Table 3) and therefore "SOCP appears to play a role in cancer, immune disorders, and infectious diseases." (Lal '104 application at page 20, lines 22-23.)

The Lal '104 application discusses a number of uses of the Lal '232 application SEQ ID NO:14 polynucleotide in addition to its use in gene expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Lal '104 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the Lal '232 application SEQ ID NO:14 polynucleotide. Consequently, my discussion in this Declaration concerning the Lal '104 application focuses on the portions of the application that relate to the use of the Lal '232 application SEQ ID NO:14 polynucleotide in gene expression monitoring applications.

10. The Lal '104 application discloses that the polynucleotide sequences disclosed therein, including the Lal '232 application SEQ ID NO:14 polynucleotide, are useful as probes in microarrays. (Lal '104 application, page 30, line 31 through page 31, line 4 and page 36, line 37 through page 37, line 14.) It further teaches that the microarrays can be used "to monitor the expression level of large numbers of genes simultaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents" (Lal '104 application at page 30, lines 31-36).

In the paragraph immediately following the Lal '104 teachings described in the preceding paragraph of this Declaration, the Lal '104 application teaches that microarrays can be prepared using the previously mentioned cDNA microarray technology developed at Stanford in

the early to mid-1990s. In this connection, the Lal '104 application specifically cites to the Schena 1996 article identified in item (a) of paragraph 7 of this Declaration (Lal '104 application at page 31, lines 1-2; *supra*, paragraph 7).

The Schena 1996 article is one of a number of documents that were published prior to the May 28, 1998 filing date of the Lal '104 application that describes the use of the Stanford-developed cDNA technology in a wide range of gene expression monitoring applications, including monitoring and analyzing gene expression patterns in human cancer. In view of the Lal '104 application, the Schena 1996 article, and other related pre-May 28, 1998 publications, persons skilled in the art on May 28, 1998 clearly would have understood the Lal '104 application to disclose the Lal '232 application SEQ ID NO:14 polynucleotide to be useful in cDNA microarrays for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 15 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development on May 28, 1998 (and for many years prior to May 28, 1998) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. Accordingly, the teachings in the Lal '104 application, in particular regarding use of the Lal '232 application SEQ ID NO:14 polynucleotide in differential gene expression analysis and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Lal '104 application on May 28, 1998 would have understood that to be so.

11. The Schena 1996 article was not the first publication that described the use of the cDNA microarray technique developed at Stanford to monitor quantitatively gene expression patterns. More than a year earlier (i.e., in October 1995), the Schena 1995 article,

titled "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray", was published (see Tabs A and B).

12. As previously discussed (*supra*, paragraphs 2 and 7), in the mid-1990s patent applications were filed in the names of Drs. Shalon and Brown that described the Stanford-developed cDNA microarray technology. The two patent documents (i.e., the Shalon PCT application and the Brown '522 patent) annexed to this Declaration at Tabs C and D evidence information that was available to the public regarding the Stanford-developed cDNA microarray technology before the May 28, 1998 filing date of the Lal '104 application.

The Shalon PCT patent application, which was published in December 1995, contains virtually the same (if not exactly the same) specification as the Brown '522 patent. Hence, the Brown '522 patent disclosure was, in effect, available to the public as of the December 1995 publication date of the Shalon PCT application (see Tabs C and D). For the sake of convenience, I cite to and discuss the Brown '522 specification below on the understanding that the descriptions in that specification were published as of the December 28, 1995 publication date of the Shalon PCT application.

The Brown '522 patent discusses, in detail, the utility of the Stanford-developed cDNA microarrays in gene expression monitoring applications. For example, in the "Summary Of The Invention" section, the Brown '522 patent teaches (see Tab D, col. 4, line 52-col. 5, line 8):

> Also forming part of the invention is a method of detecting differential expression of each of a plurality of genes in a first cell type, with respect to expression of the same genes in a second cell type. In practicing the method, there is first produced fluorescent-labeled cDNAs from mRNAs isolated from two cells types, where the cDNAs from the first and second cell types are labeled with first and second different flourescent reporters.
>
> A mixture of the labeled cDNAs from the two cell types is added to an array of polynucleotides representing a plurality of known genes derived from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array. The array is then examined by fluorescence under fluorescence excitation conditions in which (i) polynucleotides in the array that are hybridized predominantly to cDNAs derived from one of the first or second cell types give a distinct first and second fluorescence emission color, respectively, and (ii) polynucleotides in the array that are hybridized to substantially equal numbers of cDNAs derived from the first and second cell types give a distinct combined fluorescence emission color, respectively. The relative expression of known genes in the

two cell types can then be determined by the observed fluorescence emission color of each spot.

The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

13. Also pertinent to my considerations underlying this Declaration is the DeRisi article, published in December 1996. The DeRisi article describes the use of the Stanford-developed cDNA microarray technology "to analyze gene expression patterns in human cancer" (see Tab E at, e.g., page 457). The DeRisi article specifically indicates, consistent with what was apparent to persons skilled in the art in December 1996, that increasing the number of genes on the cDNA microarray permits a "more comprehensive survey of gene expression patterns," thereby enhancing the ability of the cDNA microarray to provide "new and useful insights into human biology and a deeper understanding of the gene pathways involved in the pathogenesis of cancer and other diseases" (see Tab E at page 458).

14. Other pre-May 28, 1998 publications further evidence the utility of the cDNA microarrays first developed at Stanford in a wide range of gene expression monitoring applications (see, e.g., the Shalon and the Heller articles at Tabs F and G). By no later than the March 1997 publication of the Heller article, these publications showed that employees of Synteni (i.e., James Gilmore and myself) had used the cDNA microarrays in specific gene expression monitoring applications (see Tab G).

The Heller article states that the results reported therein "successfully demonstrate the use of the cDNA microarray system as a general approach for dissecting human diseases" (Tab G at page 2150). Among other things, the Heller article describes the investigation of "1000 human genes that were randomly selected from a peripheral human blood cell library" and "[t]heir differential and quantitative expression analysis in cells of the joint tissue. . . to demonstrate the utility of the microarray method to analyze complex diseases by their pattern of gene expression" (see Tab G at pages 2150 *et seq.*).

Much of the work reported on in the Heller article was done in 1996. That article, therefore, evidences how persons skilled in the art were readily able, well prior to May 28, 1998,

to make and use cDNA microarrays to achieve highly useful results. For example, as reported in the Heller article, a cDNA microarray that was used in some of the highly successful work reported on therein was made from 1,000 genes randomly selected from a human blood cell library.

15. A person skilled in the art on May 28, 1998, who read the Lal '104 application, would understand that application to disclose the Lal '232 application SEQ ID NO:14 polynucleotide, to be highly useful as a probe for the expression of that specific polynucleotide in cDNA microarrays of the type first developed at Stanford. For example, the specification of the Lal '104 application would have led a person skilled in the art on May 28, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cancer, immune disorders, and infectious diseases to conclude that a cDNA microarray that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the Lal '232 application SEQ ID NO:14 polynucleotide. Persons skilled in the art would appreciate that a cDNA microarray that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a more useful tool than a cDNA microarray that did not contain the Lal '232 application SEQ ID NO:14 polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, and infectious diseases for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(f) below a number of reasons why a person skilled in the art, who read the Lal '104 specification on May 28, 1998, would have concluded based on that specification and the state of the art at that time, that the Lal '232 application SEQ ID NO:14 polynucleotide would be a highly useful tool for inclusion in cDNA microarrays for evaluating the efficacy and toxicity of proposed drugs for treating cancer, immune disorders, and infectious diseases, as well as for other evaluations:

(a) The Lal '104 application teaches the Lal '232 application SEQ ID NO:14 polynucleotide to be useful as a probe in cDNA microarrays of the type first developed at Stanford. It also teaches that such cDNA microarrays are useful in a number of gene expression monitoring applications, including "to develop and monitor the activities of therapeutic agents [i.e., drugs]" (see paragraph 10, *supra*).

(b) By May 28, 1998, the Stanford-developed cDNA microarray technology was a well known and widely accepted tool for use in a wide range of gene expression monitoring applications. This is evidenced, for example, by numerous publications describing the use of that cDNA technology in gene expression monitoring applications and the

fact that, for over a year, the technology had provided the basis for the operations of an up-and-running company (Synteni), with employees, that was created for the purpose of developing and commercially exploiting that technology (see paragraphs 2, 8 and 10-14, *supra*). The fact that Incyte agreed to purchase Synteni in late 1997 for an amount reported to be at least about $80 million only serves to underscore the substantial practical and commercial significance, in 1997, of the cDNA microarray technology first developed at Stanford (see paragraph 2, *supra*).

(c) The pre-May 28, 1998 publications regarding the cDNA microarray technology first developed at Stanford that I discuss in this Declaration repeatedly confirm that, consistent with the teachings in the Lal '104 application, cDNA microarrays are highly useful tools for conducting gene expression monitoring applications with respect to the development of drugs and the monitoring of their activity. Among other things, those pre-May 28, 1998 publications confirmed that cDNA microarrays (i) were useful for monitoring gene expression responses to different drugs (see paragraph 12, *supra*), (ii) were useful in analyzing gene expression patterns in human cancer, with increasing the number of genes on the cDNA microarray enhancing the ability of the cDNA microarray to provide useful information (see paragraph 13, *supra*), and (iii) were a valuable tool for use as part of a "general approach for dissecting human diseases" and for "analyz[ing] complex diseases by their pattern of gene expression" (see paragraph 14, *supra*).

(d) Based on my own extensive work for a company whose business was the development and commercial exploitation of cDNA microarray technology for more than two years prior to the May 28, 1998 filing date of the Lal '104 application, I have first-hand knowledge concerning the state of the art with respect to making and using cDNA microarrays as of May 28, 1998 (see paragraphs 2 and 14, *supra).* Persons skilled in the art as of that date would have (a) concluded that the Lal '104 application disclosed cDNA microarrays containing the Lal '232 application SEQ ID NO:14 polynucleotide to be useful, and (b) readily been able to make and use such microarrays with useful results.

(e) The Lal '104 specification contains a number of teachings that would lead persons skilled in the art on May 28, 1998 to conclude that a cDNA microarray that contained the Lal '232 application SEQ ID NO:14 polynucleotide would be a more useful tool for gene expression monitoring applications relating to drugs for treating cancer, immune disorders, and infectious diseases than a cDNA microarray that did not contain the Lal '232 application SEQ ID NO:14 polynucleotide. Among other things, the Lal '104 specification teaches that the identity of the Lal '232 application SEQ ID NO:14 polynucleotide (listed as SEQ ID NO:11 in the Lal '104 application) was determined from a uterus tissue cDNA library (UTRSNOR01) (Lal '104 application, Tables 1 and 4). Moreover, northern analysis of Lal '232

application SEQ ID NO:14 polynucleotide (listed as SEQ ID NO:11 in the Lal '104 application) shows its expression predominantly in cDNA libraries made from reproductive, cardiovascular, hematopoietic/immune, cancer-associated, inflammation-associated, and fetal tissues (Lal '104 application at Table 3) and therefore "SOCP appears to play a role in cancer, immune disorders, and infectious diseases." (Lal '104 application at page 20, lines 22-23.) . (See paragraph 9, *supra*).

(f) Persons skilled in the art on May 28, 1998 would have appreciated (i) that the gene expression monitoring results obtained using a cDNA microarray containing a probe to the Lal '232 application SEQ ID NO:14 polynucleotide would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the probe described in (i) and from the cDNA microarray as a whole (including all its other individual probes). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on May 28, 1998, having read the Lal '104 specification, would specifically request that any cDNA microarray that was being used for conducting gene expression monitoring studies on drugs for treating cancer, immune disorders, and infectious diseases (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) contain the Lal '232 application SEQ ID NO:14 polynucleotide as a probe. Persons skilled in the art on May 28, 1998 would have wanted their cDNA microarray to have a probe as described in (i) because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to May 28, 1998.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 15, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Lal '104 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the Lal '232 application SEQ ID NO:14 polynucleotide.

16. Also pertinent to my considerations underlying this Declaration is the fact that the Lal '104 disclosure regarding the uses of the Lal '232 application SEQ ID NO:14 polynucleotide for gene expression monitoring applications is <u>not</u> limited to the use of that polynucleotide as a probe in microarrays. For one thing, the Lal '104 disclosure regarding the hybridization technique used in gene expression monitoring applications is broad. (Lal '104 application at, e.g., page 4, lines 12-21.) In addition, the Lal '104 specification

repeatedly teaches that the polynucleotides described therein (including Lal '232 application SEQ ID NO:14 polynucleotide) may desirably be used as probes in any of a number of long established "standard" non-microarray techniques, such as northern analysis, for conducting gene expression monitoring studies. See, e.g.:

(a) Lal '104 application at page 7, lines 29-31 ("Northern analysis is indicative of the presence of nucleic acids encoding SOCP in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding SOCP.");

(b) Lal '104 application at page 29, lines 25-28 ("The polynucleotide sequences encoding SOCP may be used in. . . Northern analysis, dot blot, or other membrane-based technologies. . . Such qualitative or quantitative methods are well known in the art");

(c) Lal '104 application at page 30, lines 1-6 ("In order to provide a basis for the diagnosis of a disorder associated with expression of SOCP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, . . . with a sequence, or a fragment thereof, encoding SOCP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used.") (emphasis supplied); and

(d) Lal '104 application at page 34, lines 13-16 ("Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; and Ausubel, supra, ch. 4 and 16.) "

The "Sambrook et al." reference cited in item (d) immediately above is a reference that was well known to persons skilled in the art on May 28, 1998. A copy of pages from that reference manual, which was published in 1989, is annexed to this Declaration at Tab H. The attached pages from the Sambrook manual provide an overview of northern analysis and other membrane-based technologies for conducting gene expression monitoring studies that were known and used by persons skilled in the art for many years prior to the May 28, 1998 filing date of the Lal '104 application.

A person skilled in the art on May 28, 1998, who read the Lal '104 specification, would have routinely and readily appreciated that the Lal '232 application SEQ ID NO:14 polynucleotide disclosed therein would be useful as a probe to conduct gene expression monitoring analyses using northern analysis or any of the other traditional membrane-based gene expression monitoring techniques that were known and in common use many years prior to the

filing of the Lal '104 application. For example, a person skilled in the art on May 28, 1998 would have routinely and readily appreciated that the Lal '232 application SEQ ID NO:14 polynucleotide would be a useful tool in conducting gene expression analyses, using the northern analysis technique, in furtherance of (a) the development of drugs for the treatment of cancer, immune disorders, and infectious diseases, and (b) analyses of the efficacy and toxicity of such drugs.

17. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Tod Bedilion

Signed at REDWOOD CITY, California
this 1 day of JULY 2003